



THE FUTURE OF INFECTIOUS DISEASES

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Emerging infections are very much in the news and on the screen, but, regardless of that provocation, we need little reminder of the renewed importance and of the perception of importance of infectious disease for human welfare.

My admiration for people who have worked in the field or who do most of their laboratory work on dangerous pathogens runs too deep for me to pretend to be one of their number. However, I have spent five decades of research on the genetics, variability, and evolution of microbes; it is that perspective that I hope to apply to an examination of the future of infectious disease.

The cosmic drama is the competitive evolution of a species, our own, that, as symbolized in the expulsion from Eden, has eschewed biological evolution in favor of the fruits of the tree of knowledge. Our microbial competitors, on the other hand, have occupied themselves with every imaginable trick of nature: rapid genetic adaptation, mutation, and evolution.

So, I label this scenario "Wits, ours, versus genes, theirs," at least as far as further innovations will occur.

A FUNDAMENTAL QUESTION

Of course, we have evolved a very substantial repertoire of defenses, above all our immune system, or we would not be here today. But, the question is, How agile and how nimble can our wits be in exploiting what natural advantages we begin with in coping with an almost unimaginable rate of turnover of turmoil, of change, of adaptation in a very large and very diverse microbial population?

In an echo of Huntington's forecast of the clash of civilizations,¹ I would portray a critical race during the next half century, namely, between ourselves

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and microbial predators. The question might be put: Is AIDS the last-gasp pandemic, or is it the forerunner of new tidal waves of the magnitude, say, of the great plague of the 14th century?

In 50 years, perhaps a mite less, I am sure we will have developed the technology to cope with threats from microbial, even viral, infection. Slightly more optimism is needed to envisage the humanitarian, social, cultural, and political institutions needed to make that technology universally available and, indeed, have it not turn to the most malignant misapplications.

But, in the interval, many global factors have aggravated the risks. Unique in human history, we have at the same time a crowded globe and large-scale movements of people. If the Ebola outbreak in Zaire were more readily transmissible, it could easily have shown up in Dulles Airport yesterday and Cape Town, Tokyo, and Berlin tomorrow. In fact, we may have had to face the pandemic manifestations before we recognized an epicenter graced with limited public health capabilities.

In 1994, we were contemplating the same for plague in India. That displays both an egregious permission for the *Yersinia* to have established a foothold and the mounting of a successful campaign to contain it.

What if that particular strain of the plague bacteria had harbored drug-resistant plasmids, which are already endemic in many other species? Is its pneumonic manifestation associated with specific genetic adaptations? Unfortunately, there was virtually no effort to conserve primary specimens that would allow those questions to be answered.

Unique in human history, we do have the congruence of enormous impoverished human populations and near instantaneous travel of hoards of people overnight from any point on the globe to another. Thanks to the wonders of modern medicine, we also have many people living with the problems of aging and of other compromises to their immune systems; those numbers, of course, have been augmented greatly by the many tragic victims of HIV infection.

You can picture a race, as I have already noted, that involves genes versus wits, with the evolution and dissemination of the pathogens on the one side and our technical and public health defenses on the other. My first inclination was to discount human biological evolution as a process too slow and too painful to contemplate as a part of this scenario. We have to take a look at that, too, in the light of the accelerated pace of artifactual technology and of our new knowledge of direct interaction of exogenous DNA with our own genomes.

It is common wisdom, and may often be true, that the most successful pathogen is the one that eventually evolved in moderation and established a chronic

symbiotic relationship with the host. One of the most successful bacteria, perhaps the most successful, was the ancestral mitochondria that invaded some cells and engendered the first eukaryotes, conferring on them the capacity for aerobic metabolism, and likewise the blue-green alga that then emerged as the plant chloroplast.

Our own genomes embraced hundreds of integrated retrovirus sequences. We do not know if any evolved further with some mutualistic advantage to the host or whether they are merely selfish DNA baggage. Unfortunately, not every virus has such intelligent foresight, and short-term evolutionary impulses favor rapid proliferation and transmission, with many pyrrhic victories, of which our pandemics are the accidental by-products.

Besides the more popular representations that have brought these problems to broader public attention, there is a text from which I could draw most of my remarks and a large part of my own education, the study by a task force of the Institute of Medicine of emerging infections.²

These are real phenomena, not spinings of the imagination. They are not the Andromeda strain³ of some external fantasy. They are happening to us here and now.

Why has our free enterprise system failed in this particular area? We had such wonderful accomplishments through the private sector: large-scale investment, very productive development of dozens of major antibiotic discoveries. Now, suddenly, we find we are falling short. What is the source of that gap between an urgently needed market opportunity and the research and development and the investment that ought to be rushing to fill that vacuum?

MAGNITUDE OF THE PROBLEM

If we ever thought we had conquered infectious disease or even begun to in our domestic environment, that was never true worldwide. Communicable disease still remains by far the largest cause of morbidity and mortality throughout the world. But, we had invented a concept called exotic disease, which, in fact, in a world of instantaneous travel is an oxymoron. There is no way any communicable disease can be kept isolated and be kept exotic.

So, here is the race. Human evolution is too painful, too costly for us to contemplate that it will be a major factor in our further adaptation to infection. Insofar as it is driven by mutation and natural selection, on the one hand, it is very slow. On the other hand, it is very costly. Substantial changes in gene frequency require first the accidental occurrence of an appropriate adaptive mutation and then such a degree of stringency in differential reproduction,

which often, if not always, means differential mortality, as to drive those gene frequencies. That is not the way we want to go in solving our problems of adaptation to the microbial world.

There are other aspects of human evolution that have hardly been touched on in this domain. They have to do with some of the new artifactual biotechnologies. People are just beginning to talk, in the idiom of *Brave New World*,⁴ of somatic gene therapy. Perhaps as a by-product of that, we might imagine germ line introductions that would be able to proceed much more rapidly than natural selection would entail.

I do not think that is very likely to happen. I do not think that many of us would want it to go that way, but I mention it as a technical possibility. I also must remark, however, that it might happen willy-nilly. I have mentioned the dramatic change in biological evolution that was a consequence of the microbial symbiosis of a bacterium that conferred aerobic metabolism and became the mitochondria. I mentioned the hundreds of integrated retroviruses. We have seen that laboratory stocks of fruit flies throughout the world have become invaded with the so-called P. elements.⁵ They are faintly communicable. We do not understand very much about their origin. They have entered the germ line. They have been responsible for storms of mutation in many such stocks.

Remotely analogous phenomena have been observed with the ecotropic leukemia viruses in mice, and a handful of documented examples of transposition insertion in human genes tells us that human genetic change can also arise from similar sources. It is likely that the possibilities of introgressive movement of genetic material from microbes to the human could be much more rapid, resulting in much more drastic changes in human evolution than accounted for by a purely Darwinian model. It is one of the things we have to think about in our interaction with that external microbial world.

MICROBIAL EVOLUTION

It is very important to keep in mind that the problem of emerging infectious diseases is not just a clonal phenomenon. It does not depend solely on mutation within a given line of descent. If microbes and their predecessors had not already long since developed methods of genetic recombination and of reunion of metabolic pathways, they could not have possibly evolved even in a brief 4 billion years to the complexities that we have seen today.

There is promiscuous traffic of genetic material among different microbial species. It is not even confined to the microbes. There is cross-kingdom transfer, with genes moving from *Agrobacterium* into higher plants. In the laboratory,

we have seen fusions of cells between the tobacco plant and myeloma cells. There is no fundamental limit. DNA is DNA, and while there are embellishments of it that distinguish it from one kingdom to another, there can be no doubt that evolution has been substantially augmented many, many times by a crossing of the branches of the tree. It is not a simple linear progression, but promiscuous interchange is the order of the day.

We must never forget how large microbial populations are. It is not too much to think that there are 10^{14} or 10^{15} genomes of some of these entities, organisms that are capable of evolution, of drastic natural selection, of adaptation in that regard, and again of interclonal traffic. How far are they likely to go in the direction of predation, depredation, and extinction of one species? How rapidly will the coadaptations leading to relationships that are more mutualistic occur?

SCENARIO FOR THE FUTURE

My own view is that all of the above will take place, that small fluctuations will have large, chaotic effects on the final outcome, that there is no inevitability about the actual progress of a bioecological relationship. Depending very much on the chance of which mutations occur and details of the selective environment, we may see the wipeout of a host, or we may see the progressive coadaptation of the two species, which is perhaps more desirable.

Those outcomes are not necessarily always stable. They can be subject to further mutational change, leading to new flare-ups.

The contextual factors of the current status of human culture make this a particularly perilous time. In some respects, it is more dangerous than the pre-antibiotic era, when there were few defenses except isolation, which was due to the limitations of traffic. Ships might be carrying cholera, from port to port, but if voyages took weeks to complete, many diseases would run their course in that kind of an interval. Now, in 24 hours, you can go from any point you wish to name to any other.

There is good news. We do have very powerful scientific and technical tools, and the outlook is particularly bright in dealing with bacterial infection. We have not begun to exhaust the obviously visible technical opportunities that can drive a wedge between the metabolism of the parasite and the metabolism of the host. There are scores, if not hundreds, of points of difference between the details of metabolic pathways, the kind of structures that are built, and the availability of vulnerable differential targets that distinguish bacteria from humans. Many more antibacterial antibiotics remain to be discovered.

We would have to be very lucky to find more penicillins. Perhaps we have

been so spoiled by that extraordinary experience that the first successful antibiotic remains a paragon hard to match in subsequent history. Penicillin has a very broad spectrum of capacity, which is further enhanced with chemical alterations; it is not too expensive to produce and has very close to zero toxicity to the host, which, of course, has built in it the seeds of its abuse and overprescription. Why not apply it for every snuffle? What harm could it do? Just possibly, there is one chance in 100,000 of a serious bacterial infection that might be pre-empted by it.

Such broad-spectrum antibiotics, which require commonality of targets among a very broad variety of bacterial species and yet always will distinguish them from any human cellular target, will be much more difficult to find. So, the types of market opportunities that drove the glorious golden age of pharmaceutical bacterial chemotherapy may yield much thinner pickings. It has been 10 years since we have had a really exciting introduction along those lines, partly for technical reasons, but there also is generated a climate for investment that is a very poor match to the kinds of problems we are seeing today.

It may be that we will have to suffer a level of nosocomial mortality far greater than we have been accustomed to because even the 10 or 100,000 deaths a year that might otherwise have been avoidable still do not present a sufficiently large market to attract the investment needed to provide the brand new antibiotics that will have to be developed to cope with those situations.

That is an outrageous thought. It should be addressed, however, because perhaps it does hint at some sources of the failures of the market mechanism to solve all of our problems. The market mechanism is wonderful, as far as it goes. When it does not work, we ought to think of other approaches.

Viral chemotherapy presents a much bleaker landscape at the present time. A small handful of very imperfect agents is available to deal with a small repertoire of viral infections.

The intrinsic problem, of course, is far more difficult. The very fact that viruses are relatively so much simpler means they have fewer targets. The fact that they exploit the metabolism of their host to such a degree makes it more difficult to drive a wedge between them and us. We are looking for sources of specificity; we are pushed more and more to the more exquisite aspects of selectivity. For this reason, we are not going to get many broad-spectrum agents to use in that field, but we can at least design structures like Antisense, like ribozymes that would target specific sequences in viral targets. The unhappy news is that those are the easiest things for the bugs to evolve around since a small, often changeable, sequence will wipe out target specificity.

This is a kind of area that is just beginning to open. I am optimistic that, in the longer run, we will find these and other avenues of exploitation.

Perhaps even more important will be our understanding of pathways of pathogenesis. So much of the pathology of infection is a consequence of our defense mechanisms having been exploited by the invaders and going awry as far as our own health is concerned. If we could deal with the consequences of inflammatory provocation, of tumor necrosis factor, and of the other interleukins that often are responsible for the major symptomatology of microbial infection, we already would be going a long way and would, in the process, have the time to cope with the proliferation of the offending agent.

We also have to think about some very homely technologies, the low-technology modalities that we do not know much about, for controlling epidemics. What, for example, would be the role of face masks? They are, for the most part, purely symbolic. People do sometimes wear masks. They do in Japan, I know, in the course of influenza outbreaks. It is very unlikely that they do any good whatsoever. But, is it beyond imagination to think that useful barrier devices could be developed that would be applicable for home use?

We are at the very beginning of the do-it-yourself technology of knowing how to protect ourselves and of more rapid diagnosis in the doctor's office, and even at home, to better ensure the safety of food, water, and personal contacts. That could go a long way toward maintaining proper control.

The greatest danger, perhaps, is one that is being alleviated now. The complacency of the last 30 years has set the stage for the re-emergence and emergence of infectious disease. We can hope that conferences of this kind will play a part in reawakening the profession, in re-eliciting ideas that are very much needed. "Think globally, act locally" can have no better paradigm than that which applies to these circumstances.

We face a number of dilemmas in balancing the rights of individuals to be as ornery as they would like to be in their own autonomy, including their capacity to spread disease to others, and the rights and needs of the community in self-defense. We have not reached the end of our own deliberations about which policy is appropriate in those directions.

We must maintain the public health structures. I am not so optimistic that managed care is going to do it. I am told that the average period of enrollment of a given customer in a particular managed program is of the order of 3 years. Even if it is as much as 10 years, that is still a very short horizon for return on investment on the full range of preventive measures. In a competitive managed-

care system, these measures will make it beneficial for a given health maintenance organization to put in the full repertoire of preventive capability and to see it in terms of a reduction in its own health care cost. I am skeptical that a free enterprise system will work very well in that particular arena unless special care is taken to cope with it.

Finally, there is nothing deadlier than warfare for the spread of disease. In every major conflict in the past, as many casualties have arisen from infection as from bullets and bombs. There is even the awful prospect of the malicious use of biological agents in unmitigated warfare.

This conference brings together many experts to elaborate on these themes, both from the outlook of the pressing and concrete problems facing New York City and from broader national and global policy perspectives. The enormous reach of scientific and medical knowledge and institutions, and of the wisdom that may be gleaned from them, provides one resource for the future that we should use to the utmost.

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